

- (b) halo;
- (c) alkyl;
- (d) haloalkyl;
- (e) thioalkyl;
- (f) hydroxy;
- (g) amino;
- (h) alkylamino;
- (i) dialkylamino;
- (j) heteroalkyl;
- (k) optionally substituted heterocycle;
- (l) optionally substituted heterocyclylalkyl;
- (m) optionally substituted heterocyclylalkoxy;
- (n) alkylsulfonyl;
- (o) aminosulfonyl, mono-alkylaminosulfonyl or dialkylaminosulfonyl;
- (p) heteroalkoxy; and
- (q) carboxy;

R⁶ is selected from a group consisting of:

- (a) hydrogen;
- (b) halo;
- (c) alkyl; and
- (d) alkoxy; and

prodrugs, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

REMARKS

Status of the Claims

Claims 2-31 and 33-35 are pending.

Claims 8-11, 13-15 and 25-31 were objected to but found to contain allowable subject matter.

Claims 2 and 33 are amended herein.

Claims 36-39 are new claims.

Reconsideration is respectfully requested.

Initially it is gratefully acknowledged that claims 8-11, 13-15 and 25-31 were found to contain allowable subject matter, having been objected to as depending upon a rejected base claim.

Double Patenting

With regard to the double-patenting objection, a terminal disclaimer will be filed when all outstanding issues are resolved, as indicated in the previous Amendment.

Amendments to Claims 2 and 33

Claims 2 and 33 have been amended herein to recite certain selections for the group R³ found in the Examples. In claims 2 and 33, the group Z-alkylene-NR³⁰R³¹ is defined such that the alkylene group and groups R³⁰ and R³¹ (when alkyl) optionally may be substituted with one to two groups selected from OH and O(alkyl). These optional substituents are exemplified at pages 57 and 72 of the specification. In claim 33, line (w), applicant has recited the group CO₂NHR', which is exemplified at page 59 (Example 16) of the specification. These amendments to the claims are not new matter as they are supported by the examples, as referenced above.

Rejection under 35 U.S.C. §103

Claims 2-7, 12, 16-24, and 33-35 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the Faraci reference (WO 94/13643) ("Faraci").

Claim 33 herein, as well as claims 2-31 and 33-38, claim a "method of treatment of a disease in a mammal *treatable by* administration of a p38 MAP kinase inhibitor" (Emphasis added). This preamble imparts life and meaning to the claim which should be considered in analyzing patentability (*see* MPEP § 2111.02).

A *prima facie* obviousness case requires that all claim limitations be taught or suggested in the prior art. MPEP § 2143.03. No where does Faraci teach or suggest a method of

treating “a disease in a mammal treatable by administration of a p38 MAP kinase inhibitor. ...” Additionally, nowhere does Faraci teach or suggest a method of inhibiting the activity of a p38 MAP kinase in a mammal (*see* claim 39). While Faraci makes a general reference to the treatment of inflammatory conditions, when Faraci is properly considered *as a whole* it is clear that it does not purport to teach the treatment of all inflammatory conditions but instead, the use of its compounds as corticotropin-releasing factor (CRF) antagonists for treating stress-induced or stress-related conditions. Thus, for example, Faraci does not teach or suggest the treatment of inflammatory conditions such as arthritis (*e.g.*, rheumatoid arthritis or osteoarthritis), adult respiratory distress syndrome, or asthma (*cf.* Specification herein, at pp. 1-2 and claims 35-38).

In assessing the obviousness of the instantly-claimed invention, a first step is to determine the scope and content of the prior art *as a whole*, including such factors as the size of the prior art genus, the structure of the disclosed species, the physical properties of the compounds, and the number of species that fall within the genus. *See* MPEP § 2144.08 (II) (a)(1). Then, the differences between the prior art and claimed invention should be considered. Next, a determination should be made whether one skilled in the field would have been motivated to discover the claimed invention.

Applying the first step, Faraci recites a method of treating CRF-related conditions with a broad genus of pyrazole-based compounds, having an untold number of species. In support of its claimed utility, Faraci relies upon US Pat. Nos. 4,605,642 and 5,063,245, incorporated by reference. Notably, as suggested in Faraci and explained in the ‘642 and ‘245 patents, CRF antagonists are considered effective in treating stress-induced disorders. For example, the ‘642 patent describes the utility of CRF antagonists as follows:

CRF has significant effects on the brain as a mediator of many of the body’s stress responses. Accordingly, CRF antagonists delivered to the brain should also find application in modifying the mood, learning and behavior of normal and mentally disordered individuals. Furthermore, CRF antagonists in the brain could ameliorate stress-induced conditions to which endogenous CRF might contribute, including some types of hypertension, infertility, decreased libido, impotency and hyperglycemia [P]eripherally administered CRF antagonists ... may be used to ... influence memory, mood, pain appreciation, etc., and more specifically alertness, depression, and/or anxiety, as well as to modulate the immune system, gastrointestinal tract, and adrenalcortical growth and function. [col. 12, lines 42-61].

The '245 patent describes the utility of CRF antagonists as follows:

[E]vidence from a variety of sources indicates that the use of centrally-active CRF receptor antagonists can be useful in the treatment of depression. In addition, substantial data indicate that such compounds can be useful in the treatment of a number of other stress-related disorders including anxiety, panic disorder, obsessive-compulsive disorder, abnormal aggression, stress-induced cardiovascular abnormalities (e.g., unstable angina and reactive hypertension), anorexia nervosa, bulimia and irritable bowel syndrome. CRF antagonists also find utility in treating psychologically or physically induced stress-mediate immune suppression associated with a number of disease states. [US Pat. 5,063,245 at col. 5, lines 5-18].

Faraci describes his claimed method as follows:

The invention further includes a method for the treatment of illnesses induced or facilitated by corticotropin releasing factor by administering to a subject in need of such treatment a compound of formula I or the known compound, both as defined above, and a method for the treatment of *stress-induced* depression and headache, abdominal bowel syndrome, inflammatory disorders, immune suppression, HIV infections, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa, hemorrhagic stress, drug and alcohol withdrawal symptoms, drug addiction, and fertility problems, particularly depression (page 5, lines 1-8).

In contrast, the instant invention relates to methods of treating diseases treatable by inhibition of p38 kinase, which are not suggested Faraci. As noted above, Faraci does not teach or suggest treatment of diseases such as rheumatoid arthritis, osteoarthritis, adult respiratory distress syndrome, asthma (*see* claims 35-38), or various other diseases treatable by inhibition of p38. Moreover, there are differences in the description of useful compounds in Faraci as compared with the genus defined herein. Faraci discloses a large genus of pyrazole-based compounds and recites preferred selections as a 3-methylthio group, a 4-position phenyl in turn substituted at the 2-position (more preferably with Cl), and a 1-position phenyl having three small group substituents, such as Cl, Br, CF₃, CH₃, OCH₃, and the like. (*See* generally Faraci at pp. 31-47). The instant application recites a different genus of compounds where the group R² is not methylthio, where the 1-position phenyl has two optional substituents, and where the 4-aryloxy group has a mandatory R³ substituent as defined herein.. One skilled in the field would not predict that this different, more particularly defined genus of pyrazole-based compounds,

having different selections for the various substituents thereon, would have activity in inhibiting p38 kinase and be effective in the treatment of p38 mediated diseases.

Accordingly, applicant requests that the obviousness rejection be withdrawn because all limitations of the instantly-pending claims are not taught or suggested in Faraci, and further, one skilled in the field would not be motivated by Faraci to develop a method of treating diseases treatable by inhibition of p38MAP kinase inhibitors with the genus of compounds recited herein.

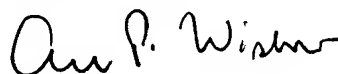
FEES

No fees should be due. Although four new claims are added, including an independent claim, in the last Office Action five claims were canceled, and the case contains less than three independent claims. However, in the event it is determined that a fee is due, please charge same to Deposit Account No. 18-1700.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-852-1141. For the Examiner's convenience, a full set of the claims as pending should the instant amendments be entered is attached as Appendix B.

Respectfully submitted,



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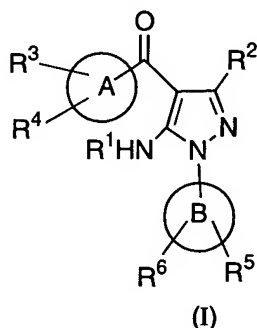
APPENDIX A
VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 2 and 33 have been amended as follows.

2. (Twice Amended) The method of Claim 33 wherein R³ is:
- (a) optionally substituted heterocyclyl;
 - (b) aryl or heteroaryl both optionally substituted with a substituent selected from halo, alkyl, amino, alkoxy, carboxy, lower alkoxy carbonyl, SO₂R' (where R' is alkyl) or SO₂NR'R'' (where R' and R'' are independently hydrogen or alkyl);
 - (c) heteroalkyl;
 - (d) heteroalkenyl;
 - (e) heteroalkoxy;
 - (f) optionally substituted heterocyclylalkyl or heterocyclylloxy;
 - (g) optionally substituted heterocyclylalkenyl;
 - (h) optionally substituted heterocyclylalkynyl;
 - (i) optionally substituted heterocyclylalkoxy;
 - (j) optionally substituted heterocyclylalkylamino;
 - (k) optionally substituted heterocyclylalkylcarbonyl;
 - (l) -Y-(alkylene)-R⁹ where Y is a single bond, -O- or -NH- and R⁹ is optionally substituted heteroaryl, -CONR¹²R¹³, -SO₂R¹⁴, -SO₂NR¹⁵R¹⁶, -NHSO₂R¹⁷ or -NHSO₂NR¹⁸R¹⁹ where R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸ and R¹⁹ are independently of each other hydrogen, alkyl or heteroalkyl;
 - (m) cycloalkylalkyl, cycloalkylalkynyl and cycloalkylalkynyl, all optionally substituted with alkyl, halo, hydroxy or amino;
 - (n) arylaminoalkylene or heteroarylaminoalkylene; or
 - (o) Z-alkylene-NR³⁰R³¹ where Z is -NH-, -N(alkyl)- or -O-, and R³⁰ and R³¹ are independently of each other, hydrogen, alkyl or heteroalkyl, wherein

said alkylene and alkyl groups are optionally substituted with one to two groups selected from OH and O(alkyl).

33. (Twice Amended) A method of treatment of a disease in a mammal treatable by administration of a p38 MAP kinase inhibitor, comprising administration to the mammal a therapeutically effective amount of a compound selected from the group of compounds represented by Formula (I):



wherein:

R¹ is hydrogen or acyl;

R² is hydrogen or alkyl;

A is an aryl ring;

B is an aryl ring;

R³ is selected from the group consisting of:

- (a) acylamino;
- (b) optionally substituted heterocyclyl;
- (c) optionally substituted aryl or heteroaryl;
- (d) heteroalkenyl;
- (e) heteroalkynyl;
- (f) heteroalkoxy;
- (g) optionally substituted heterocyclylalkyl;
- (h) optionally substituted heterocyclylalkenyl;
- (i) optionally substituted heterocyclylalkynyl;

- (j) optionally substituted heterocyclalkoxy, cycloxy, or heterocycloxy;
- (k) optionally substituted heterocyclalkylamino;
- (l) optionally substituted heterocyclalkylcarbonyl;
- (m) $\text{-NHSO}_2\text{R}^6$ where R^6 is optionally substituted heterocyclalkyl;
- (n) $\text{-NHSO}_2\text{NR}^7\text{R}^8$ where R^7 and R^8 are, independently of each other, hydrogen, alkyl or heteroalkyl;
- (o) -Y-(alkylene)-R^9 where:
Y is a single bond, -O- , -NH- or $\text{-S(O)}_n\text{-}$ (where n is an integer from 0 to 2); and R^9 is cyano, optionally substituted heteroaryl, -COOH , -COR^{10} , -COOR^{11} , $\text{-CONR}^{12}\text{R}^{13}$, $\text{-SO}_2\text{R}^{14}$, $\text{-SO}_2\text{NR}^{15}\text{R}^{16}$, $\text{-NHSO}_2\text{R}^{17}$ or $\text{-NHSO}_2\text{NR}^{18}\text{R}^{19}$, where R^{10} is optionally substituted heterocycle, R^{11} is alkyl, and R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} and R^{19} are, independently of each other, hydrogen, alkyl or heteroalkyl;
- (p) $\text{-C(=NR}^{20}\text{)(NR}^{21}\text{R}^{22})$ where R^{20} , R^{21} and R^{22} independently represent hydrogen, alkyl or hydroxy, or R^{20} and R^{21} together are $\text{-(CH}_2\text{)}_n\text{-}$ where n is 2 or 3 and R^{22} is hydrogen or alkyl;
- (q) $\text{-NHC(=X)NR}^{23}\text{R}^{24}$ where X is O or S, and R^{23} and R^{24} are, independently of each other, hydrogen, alkyl or heteroalkyl;
- (r) $\text{-CONR}^{25}\text{R}^{26}$ where R^{25} and R^{26} independently represent hydrogen, alkyl, heteroalkyl or optionally substituted heterocyclalkyl, or R^{25} and R^{26} together with the nitrogen to which they are attached form an optionally substituted heterocycl ring;
- (s) $\text{-S(O)}_n\text{R}^{27}$ where n is an integer from 0 to 2, and R^{27} is optionally substituted heterocyclalkyl;
- (t) cycloalkylalkyl, cycloalkylalkynyl and cycloalkylalkynyl, all optionally substituted with alkyl, halo, hydroxy or amino;
- (u) arylaminoalkylene or heteroaryl aminoalkylene;

- (v) Z-alkylene-NR³⁰R³¹ or Z-alkylene-OR³² where Z is -O-, and R³⁰, R³¹ and R³² are independently of each other, hydrogen, alkyl or heteroalkyl, wherein said alkylene and alkyl groups are optionally substituted with one to two groups selected from OH and O(alkyl);
- (w) -OC(O)-alkylene-CO₂H, or -OC(O)-NR'R'' , or CO₂NHR' (where R' and R'' are independently hydrogen or alkyl); and
- (x) heteroarylalkenylene or heteroarylalkynylene;

R⁴ is selected from the group consisting of:

- (a) hydrogen;
- (b) halo;
- (c) alkyl;
- (d) alkoxy; and
- (e) hydroxy;

R⁵ is selected from the group consisting of:

- (a) hydrogen;
- (b) halo;
- (c) alkyl;
- (d) haloalkyl;
- (e) thioalkyl;
- (f) hydroxy;
- (g) amino;
- (h) alkylamino;
- (i) dialkylamino;
- (j) heteroalkyl;
- (k) optionally substituted heterocycle;
- (l) optionally substituted heterocyclalkyl;
- (m) optionally substituted heterocyclalkoxy;
- (n) alkylsulfonyl;
- (o) aminosulfonyl, mono-alkylaminosulfonyl or dialkylaminosulfonyl;

- (p) heteroalkoxy; and
- (q) carboxy;

R⁶ is selected from a group consisting of:

- (a) hydrogen;
- (b) halo;
- (c) alkyl; and
- (d) alkoxy; and

prodrugs, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

APPENDIX B
PENDING CLAIMS

2. (Amended Herein) The method of Claim 33 wherein R³ is:
- (a) optionally substituted heterocyclyl;
 - (b) aryl or heteroaryl both optionally substituted with a substituent selected from halo, alkyl, amino, alkoxy, carboxy, lower alkoxy carbonyl, SO₂R' (where R' is alkyl) or SO₂NR'R'' (where R' and R'' are independently hydrogen or alkyl);
 - (c) heteroalkyl;
 - (d) heteroalkenyl;
 - (e) heteroalkoxy;
 - (f) optionally substituted heterocyclylalkyl or heterocyclyloxy;
 - (g) optionally substituted heterocyclylalkenyl;
 - (h) optionally substituted heterocyclylalkynyl;
 - (i) optionally substituted heterocyclylalkoxy;
 - (j) optionally substituted heterocyclylalkylamino;
 - (k) optionally substituted heterocyclylalkylcarbonyl;
 - (l) -Y-(alkylene)-R⁹ where Y is a single bond, -O- or -NH- and R⁹ is optionally substituted heteroaryl, -CONR¹²R¹³, -SO₂R¹⁴, -SO₂NR¹⁵R¹⁶, -NHSO₂R¹⁷ or -NHSO₂NR¹⁸R¹⁹ where R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸ and R¹⁹ are independently of each other hydrogen, alkyl or heteroalkyl;
 - (m) cycloalkylalkyl, cycloalkylalkynyl and cycloalkylalkynyl, all optionally substituted with alkyl, halo, hydroxy or amino;
 - (n) arylaminoalkylene or heteroarylaminoalkylene; or
 - (o) Z-alkylene-NR³⁰R³¹ where Z is -NH-, -N(alkyl)- or -O-, and R³⁰ and R³¹ are independently of each other, hydrogen, alkyl or heteroalkyl, wherein

said alkylene and alkyl groups are optionally substituted with one to two groups selected from OH and O(alkyl).

3. The method of Claim 2 wherein R^1 and R^2 are hydrogen; and B is phenyl.
4. The method of Claim 3 wherein A is phenyl.
5. The method of Claim 4 wherein R^4 is hydrogen; and R^5 is halo or alkyl.
6. The method of Claim 5 wherein R^5 is chloro, fluoro or methyl; and R^6 is hydrogen, chloro, fluoro, methyl or methoxy.
7. The method of Claim 5, wherein R^3 is optionally substituted heteroaryl.
8. The method of Claim 7, wherein R^3 is pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, N-oxidopyridin-2-yl, N-oxidopyridin-3-yl, N-oxidopyridin-4-yl or pyridon-2-yl, all optionally substituted.
9. The method of Claim 8, wherein R^3 is at the 3-position.
10. The method of Claim 9, wherein R^5 is 4-F and R^6 is hydrogen.
11. The method of Claim 9, wherein R^5 is 2-Me and R^6 is hydrogen.
12. The method of Claim 5, wherein R^3 is optionally substituted phenyl.
13. The method of Claim 12, wherein R^3 is 3-sulfamoylphenyl, 3-methylsulfonylphenyl, 3-carboxyphenyl or 3-ethoxycarbonylphenyl.
14. The method of Claim 13, wherein R^3 is at the 3-position.
15. The method of Claim 14, wherein R^5 is 4-F and R^6 is hydrogen.
16. The method of Claim 5, wherein R^3 is:

- (a) heteroalkyl;
- (b) heteroalkoxy;
- (c) optionally substituted heterocyclalkyl;
- (d) optionally substituted heterocyclalkoxy;
- (e) optionally substituted heterocyclalkylamino;
- (f) -Y-(alkylene)-R⁹ where Y is a single bond, -O- or -NH- and R⁹ is optionally substituted heteroaryl, -CONR¹²R¹³, SO₂R¹⁴, -SO₂NR¹⁵R¹⁶, -NHSO₂R¹⁷ or -NHSO₂NR¹⁸R¹⁹ where R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸ and R¹⁹ are independently of each other hydrogen, alkyl or heteroalkyl; or
- (g) Z-alkylene-NR³⁰R³¹ where Z is -NH-, -N(alkyl)- or -O-, and R³⁰ and R³¹ are independently of each other, hydrogen, alkyl or heteroalkyl.

22. The method of Claim 16, wherein R³ is heteroalkoxy.

23. The method of Claim 22, wherein R³ is at the 3-position and is selected from the group consisting of 3-dimethylaminopropoxy, 2-dimethylaminoethoxy, 2-hydroxyethoxy, 2,3-dihydroxypropoxy, and 2,2-(dihydroxymethyl)ethoxy.

24. The method of Claim 23 wherein R⁵ is 4-F or 2-Me and R⁶ is hydrogen.

25. The method of Claim 16, wherein R³ is optionally substituted heterocyclalkyl, optionally substituted heterocyclalkoxy or optionally substituted heterocyclalkylamino.

26. The method of Claim 25, wherein R³ is at the 3-position and is selected from the group consisting of 3-(morpholin-4-yl)propoxy, 2-(morpholin-4-yl)ethoxy, 2-(2-oxo-pyrrolidin-1-yl)ethoxy, 3-(morpholin-4-yl)propyl, 2-(morpholin-4-yl)ethyl, 4-(morpholin-4-yl)butyl, 3-(morpholin-4-yl)propylamino, 2-(morpholin-4-yl)ethylamino, 4-hydroxy-piperidinylmethyl, 2-(S,S-dioxo-thiamorpholin-4-yl)ethyl, 3-(S,S-dioxo-thiamorpholin-4-yl)propyl and N-methylpiperazinylmethyl.

27. The method of Claim 26 wherein R^5 is 4-F or 2-Me and R^6 is hydrogen.

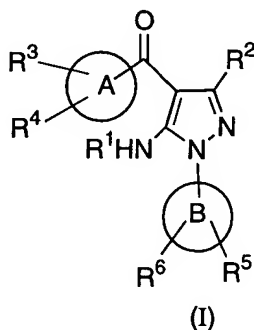
28. The method of Claim 16 wherein R^3 is
-Y-(alkylene)- R^9 where Y is a single bond, -O- or -NH- and R^9 is optionally substituted
heteroaryl, -CONR¹²R¹³, -SO₂R¹⁴, -SO₂NR¹⁵R¹⁶, -NHSO₂R¹⁷ or -NHSO₂NR¹⁸R¹⁹ where R^{12} , R^{13} ,
 R^{14} , R^{15} , R^{16} , R^{17} , R^{18} and R^{19} are independently of each other hydrogen, alkyl or heteroalkyl.

29. The method of Claim 28, wherein Y is a single bond and R^9 is -SO₂R¹⁴ or
-SO₂NR¹⁵R¹⁶.

30. The method of Claim 29 wherein R^3 is methylsulfonylethyl or
sulfamoylethyl.

31. The method of Claim 30 wherein R^5 is 4-F or 2-Me and R^6 is hydrogen.

33. (Amended Herein) A method of treatment of a disease in a mammal
treatable by administration of a p38 MAP kinase inhibitor, comprising administration to the
mammal a therapeutically effective amount of a compound selected from the group of
compounds represented by Formula (I):



wherein:

R^1 is hydrogen or acyl;
 R^2 is hydrogen or alkyl;
A is an aryl ring;

B is an aryl ring;

R³ is selected from the group consisting of:

- (a) acylamino;
- (b) optionally substituted heterocyclyl;
- (c) optionally substituted aryl or heteroaryl;
- (d) heteroalkenyl;
- (e) heteroalkynyl;
- (f) heteroalkoxy;
- (g) optionally substituted heterocyclalkyl;
- (h) optionally substituted heterocyclalkenyl;
- (i) optionally substituted heterocyclalkynyl;
- (j) optionally substituted heterocyclalkoxy, cyclyloxy, or heterocyclloxy;
- (k) optionally substituted heterocyclalkylamino;
- (l) optionally substituted heterocyclalkylcarbonyl;
- (m) -NHSO₂R⁶ where R⁶ is optionally substituted heterocyclalkyl;
- (n) -NHSO₂NR⁷R⁸ where R⁷ and R⁸ are, independently of each other, hydrogen, alkyl or heteroalkyl;
- (o) -Y-(alkylene)-R⁹ where:
Y is a single bond, -O-, -NH- or -S(O)_n- (where n is an integer from 0 to 2); and R⁹ is cyano, optionally substituted heteroaryl, -COOH, -COR¹⁰, -COOR¹¹, -CONR¹²R¹³, -SO₂R¹⁴, -SO₂NR¹⁵R¹⁶, -NHSO₂R¹⁷ or -NHSO₂NR¹⁸R¹⁹, where R¹⁰ is optionally substituted heterocycle, R¹¹ is alkyl, and R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸ and R¹⁹ are, independently of each other, hydrogen, alkyl or heteroalkyl;
- (p) -C(=NR²⁰)(NR²¹R²²) where R²⁰, R²¹ and R²² independently represent hydrogen, alkyl or hydroxy, or R²⁰ and R²¹ together are - (CH₂)_n- where n is 2 or 3 and R²² is hydrogen or alkyl;

- (q) $-\text{NHC}(=\text{X})\text{NR}^{23}\text{R}^{24}$ where X is O or S, and R^{23} and R^{24} are, independently of each other, hydrogen, alkyl or heteroalkyl;
- (r) $-\text{CONR}^{25}\text{R}^{26}$ where R^{25} and R^{26} independently represent hydrogen, alkyl, heteroalkyl or optionally substituted heterocyclalkyl, or R^{25} and R^{26} together with the nitrogen to which they are attached form an optionally substituted heterocycl ring;
- (s) $-\text{S}(\text{O})_n\text{R}^{27}$ where n is an integer from 0 to 2, and R^{27} is optionally substituted heterocyclalkyl;
- (t) cycloalkylalkyl, cycloalkylalkynyl and cycloalkylalkynyl, all optionally substituted with alkyl, halo, hydroxy or amino;
- (u) arylaminoalkylene or heteroarylaminomalkylene;
- (v) Z-alkylene- $\text{NR}^{30}\text{R}^{31}$ or Z-alkylene- OR^{32} where Z is -O-, and R^{30} , R^{31} and R^{32} are independently of each other, hydrogen, alkyl or heteroalkyl, wherein said alkylene and alkyl groups are optionally substituted with one to two groups selected from OH and O(alkyl);
- (w) $-\text{OC}(\text{O})\text{-alkylene-CO}_2\text{H}$, $-\text{OC}(\text{O})\text{-NR}'\text{R}''$, or $\text{CO}_2\text{NHR}'$ (where R' and R'' are independently hydrogen or alkyl); and
- (x) heteroarylalkenylene or heteroarylalkynylene;

R^4 is selected from the group consisting of:

- (a) hydrogen;
- (b) halo;
- (c) alkyl;
- (d) alkoxy; and
- (e) hydroxy;

R^5 is selected from the group consisting of:

- (a) hydrogen;
- (b) halo;
- (c) alkyl;
- (d) haloalkyl;

- (e) thioalkyl;
- (f) hydroxy;
- (g) amino;
- (h) alkylamino;
- (i) dialkylamino;
- (j) heteroalkyl;
- (k) optionally substituted heterocycle;
- (l) optionally substituted heterocyclalkyl;
- (m) optionally substituted heterocyclalkoxy;
- (n) alkylsulfonyl;
- (o) aminosulfonyl, mono-alkylaminosulfonyl or dialkylaminosulfonyl;
- (p) heteroalkoxy; and
- (q) carboxy;

R⁶ is selected from a group consisting of:

- (a) hydrogen;
- (b) halo;
- (c) alkyl; and
- (d) alkoxy; and

prodrugs, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

34. The method of Claim 33 wherein the disease is an inflammatory disease.

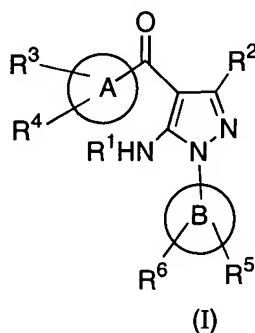
35. The method of Claim 34 wherein the disease is arthritis.

36. (New Herein). The method of Claim 35 wherein the disease is rheumatoid arthritis.

37. (New Herein). The method of Claim 33 wherein the disease is adult respiratory distress syndrome.

38. (New Herein) The method of Claim 33 wherein the disease is asthma.

39. (New Herein). A method of inhibiting the activity of a p38 MAP kinase in a mammal, comprising administration to the mammal a therapeutically effective amount of a compound selected from the group of compounds represented by Formula (I):



wherein:

R^1 is hydrogen or acyl;

R^2 is hydrogen or alkyl;

A is an aryl ring;

B is an aryl ring;

R^3 is selected from the group consisting of:

- (a) acylamino;
- (b) optionally substituted heterocyclyl;
- (c) optionally substituted aryl or heteroaryl;
- (d) heteroalkenyl;
- (e) heteroalkynyl;
- (f) heteroalkoxy;
- (g) optionally substituted heterocyclylalkyl;
- (h) optionally substituted heterocyclylalkenyl;
- (i) optionally substituted heterocyclylalkynyl;

- (j) optionally substituted heterocyclalkoxy, cycloxy, or heterocycloxy;
- (k) optionally substituted heterocyclalkylamino;
- (l) optionally substituted heterocyclalkylcarbonyl;
- (m) $\text{-NHSO}_2\text{R}^6$ where R^6 is optionally substituted heterocyclalkyl;
- (n) $\text{-NHSO}_2\text{NR}^7\text{R}^8$ where R^7 and R^8 are, independently of each other, hydrogen, alkyl or heteroalkyl;
- (o) -Y-(alkylene)-R^9 where:
Y is a single bond, -O- , -NH- or $\text{-S(O)}_n\text{-}$ (where n is an integer from 0 to 2); and R^9 is cyano, optionally substituted heteroaryl, -COOH , -COR^{10} , -COOR^{11} , $\text{-CONR}^{12}\text{R}^{13}$, $\text{-SO}_2\text{R}^{14}$, $\text{-SO}_2\text{NR}^{15}\text{R}^{16}$, $\text{-NHSO}_2\text{R}^{17}$ or $\text{-NHSO}_2\text{NR}^{18}\text{R}^{19}$, where R^{10} is optionally substituted heterocycle, R^{11} is alkyl, and R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} and R^{19} are, independently of each other, hydrogen, alkyl or heteroalkyl;
- (p) $\text{-C(=NR}^{20}\text{)(NR}^{21}\text{R}^{22})$ where R^{20} , R^{21} and R^{22} independently represent hydrogen, alkyl or hydroxy, or R^{20} and R^{21} together are $\text{-(CH}_2\text{)}_n\text{-}$ where n is 2 or 3 and R^{22} is hydrogen or alkyl;
- (q) $\text{-NHC(=X)NR}^{23}\text{R}^{24}$ where X is O or S, and R^{23} and R^{24} are, independently of each other, hydrogen, alkyl or heteroalkyl;
- (r) $\text{-CONR}^{25}\text{R}^{26}$ where R^{25} and R^{26} independently represent hydrogen, alkyl, heteroalkyl or optionally substituted heterocyclalkyl, or R^{25} and R^{26} together with the nitrogen to which they are attached form an optionally substituted heterocycl ring;
- (s) $\text{-S(O)}_n\text{R}^{27}$ where n is an integer from 0 to 2, and R^{27} is optionally substituted heterocyclalkyl;
- (t) cycloalkylalkyl, cycloalkylalkynyl and cycloalkylalkynyl, all optionally substituted with alkyl, halo, hydroxy or amino;
- (u) arylaminoalkylene or heteroarylaminomethylene;

- (v) Z-alkylene-NR³⁰R³¹ or Z-alkylene-OR³² where Z is -O-, and R³⁰, R³¹ and R³² are independently of each other, hydrogen, alkyl or heteroalkyl, wherein said alkylene and alkyl groups are optionally substituted with one to two groups selected from OH and O(alkyl);
- (w) -OC(O)-alkylene-CO₂H, -OC(O)-NR'R'', or CO₂NHR' (where R' and R'' are independently hydrogen or alkyl); and
- (x) heteroarylalkenylene or heteroarylalkynylene;

R⁴ is selected from the group consisting of:

- (a) hydrogen;
- (b) halo;
- (c) alkyl;
- (d) alkoxy; and
- (e) hydroxy;

R⁵ is selected from the group consisting of:

- (a) hydrogen;
- (b) halo;
- (c) alkyl;
- (d) haloalkyl;
- (e) thioalkyl;
- (f) hydroxy;
- (g) amino;
- (h) alkylamino;
- (i) dialkylamino;
- (j) heteroalkyl;
- (k) optionally substituted heterocycle;
- (l) optionally substituted heterocyclalkyl;
- (m) optionally substituted heterocyclalkoxy;
- (n) alkylsulfonyl;
- (o) aminosulfonyl, mono-alkylaminosulfonyl or dialkylaminosulfonyl;

(p) heteroalkoxy; and

(q) carboxy;

R^6 is selected from a group consisting of:

(a) hydrogen;

(b) halo;

(c) alkyl; and

(d) alkoxy; and

prodrugs, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.